VERSION WITH MARKINGS TO SHOW CHANGES MADE
PURSUANT TO 37 C.F.R. §§1.121(b)

In the Specification:

The paragraph beginning at page 13, line 22, has been amended as follows:

Figure 2 is a histogram depicting transformation efficiencies obtained using the apparatus of Figure 1 to deliver DNA particles at 30 bar pressure over a 60 mm target distance as described in [the] Example 1. In the Figure, "B/P" refers to transformation efficiency (expressed as the number of blue cells / per culture dish), "F#2" and "F#3" refer to preparation 2 and preparation 3, respectively, "TCC" refers to the contemporaneous delivery of DNA-coated tungsten particles, and "THC" refers to a historical delivery of DNA-coated tungsten particles.

The paragraph beginning at page 13, line 22, has been amended as follows:

Figure 3 is a graph depicting the transformation efficiencies obtained using the apparatus of Figure 1 to deliver DNA particles at 30 bar pressure over a range of target distances, also as described in [the] Example 1. In the Figure, "B/P" refers to transformation efficiency (expressed as the number of blue cells / per culture dish), and "d(mm)" refers to target distance expressed in mm.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

PURSUANT TO 37 C.F.R. §§1.121(c)

In the Claims:

Claim 24 has been amended as follows:

24. (Amended) A method according to claim 15, wherein size reducing of the compacted material is carried out by milling, [and/or] sieving, or a combination of milling and sieving.

Claim 40 has been amended as follows:

40. (Amended) A method of delivering a selected pharmaceutical agent to a vertebrate subject, said method comprising providing a compacted particulate pharmaceutical preparation according to claim [40]37 and delivering the preparation to a target tissue or cell of the vertebrate subject by needleless syringe.

REMARKS

Introductory Comments:

Claims 1-40 were pending in the application. Claims 1-14 have been withdrawn from further consideration pursuant to 37 C.F.R. §1.142(b) as drawn to a non-elected invention. Thus, claims 15-40 were examined in the Office Action dated 26 December 2000. Applicants note with appreciation that the Office has acknowledged applicants' claim to foreign priority to the 11 June 1996 and 11 September 1996 Great Britain applications. Applicants will submit certified copies of the above-referenced priority applications under separate cover. In the Action, the Office has objected to the specification as informal. In addition, the following claim rejections have been entered: (1) claims 15-37, 39 and 40 were rejected under 35 U.S.C. §112, first paragraph, as nonenabled; (2) claims 24 and 40 were rejected under 35 U.S.C. §112, second paragraph as indefinite; and (3) claim 38 was rejected under 35 U.S.C. §102(b) as unpatentable over U.S. Patent No. 5,100,792 to Sanford et al. ("Sanford"). Claims 1-37 and 39-40 have been deemed to be clear from the prior art.

The objection to the specification and the claim rejections are traversed for the following reasons.

Overview of the Amendment:

The specification has been amended to correct the informalities helpfully pointed out by the Office. More particularly, the description of Figures 2 and 3 has been amended to define the abbreviations used in those figures, that is, to define "B/P", "F#2", "F#3", "TCC" and "THC" as requested by the Office. Support for these amendments can be found in the specification and figures as originally filed, and particularly in the specification at page 39, line 23 through page 44, line 25.

Accordingly no new matter has been entered by way of the amendment to the specification, and the entry thereof is respectfully requested.

In addition, claims 24 and 40 have been amended to correct editorial errors and to clear up matters of form. More particularly, claim 24 has been amended to now recite that the size reduction step can entail milling, sieving, or a combination of milling and sieving (i.e., milling and/or sieving) to clear up a matter of form. Support for the amendment can be found in the claim as originally filed. Claim 40 has been amended to correct an obvious editorial error in the recited dependancy.

Accordingly no new matter has been entered by way of the amendment to the claims, and the entry thereof is respectfully requested.

Attached herein above are marked-up versions of the changes made to the specification and claims by the current amendment. The attached pages are captioned "Version With Markings to Show Changes Made."

The Objection to the Specification:

The specification was objected to as informal with respect to the brief description of Figures 2 and 3. Appropriate correction was required.

In response, applicants draw the Office's attention to the above amendment to the specification, wherein the required changes have been made. Reconsideration and withdrawal of the objection is thus respectfully requested.

The Rejections Under 35 U.S.C. §112, first paragraph:

Claims 15-37, 39 and 40 were rejected under 35 U.S.C. §112, first paragraph, as nonenabled. The Office asserts that the rejected claims "contain subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Applicants respectfully disagree.

Scope of enablement for claims 15-28. Claims 15-28 recite methods for forming densified particles from a particulate pharmaceutical preparation, wherein the densified particles are suitable for transdermal delivery using needleless injection. Claims 15-26 are not limited by a particular class of pharmaceutical, and claims 15-28 are most certainly not limited to a particular use of the converted pharmaceuticals. Claims 27 and 28 are limited to methods for forming densified particles from a peptide/protein or gene construct pharmaceuticals, respectively. Applicants have described in great detail how to practice these recited methods throughout their entire scope, and the blanket rejection of these claims under the current Office Action is deemed inappropriate and simply not supported by the record.

More particularly, applicants have provided detailed directions regarding how to convert a starting particulate pharmaceutical composition into densified particles, and how to assess those particles. See, e.g., applicants' specification at page 31, line 14 through page 34, line 16 and page 33, line 26 through page 36, line 3. Detailed directions are also provided regarding how to take the densified particles and administer them using needleless injection. See, e.g., applicants' specification at page 37, line 5 through page 39, line 9.

In addition to the above-noted detailed description regarding both how to practice the densification and the administration steps of claims 15-28, applicants have also provided numerous working examples regarding these techniques. In Examples 1 and 2 (page 39, line 24 through page 47, line 7), applicants provided working examples of how to make densified DNA compositions using the methods of the invention, and then how to administer those compositions using needleless injection. In Examples 3-5 (page 47, line 10 through page 50, line 9), applicants provided

working examples of how to make densified recombinant protein compositions using the methods of the invention, and then how to administer those compositions using needleless injection. And in Examples 8 and 9 (page 53, line 5 through page 55, line 27), applicants provided working examples of how to make densified particulate compositions from commonly used pharmaceutical excipients using the methods of the invention.

In other words, applicants have provided sufficient guidance to the skilled artisan with respect to how to make and use applicants' recited methods of claims 15-28, and are thus in full compliance with Section 112. Accordingly, the Office's assertion that these claims are not enabled is simply not supported by any fair reading of applicants detailed description of the invention, particularly when read in light of the numerous working examples provided therein. As long as applicants' specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the scope of the claims, then the enablement requirement of 35 U.S.C. §112, first paragraph, is met. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Applicants' specification contains detailed disclosure of numerous ways of carrying out the recited densification steps required by claims 15-28, as well as a number of ways for carrying out the needleless injection step. Accordingly, the enablement requirement has been met for these claims. In addition, if applicants' specification contains within it a connotation of how to use the invention, and the art recognizes that standard modes of administration are known and contemplated (e.g., needleless injection techniques), then 35 U.S.C. §112, first paragraph, is satisfied. See *In re Johnson*, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 144 USPQ 637,643 (CCPA 1965); and see also *In re Brana*, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993). For all of these reasons, then, the rejection of claims 15-

28 under 35 U.S.C. §112, first paragraph is improper and simply not supported by the record. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Scope of enablement for claims 29-37. Claims 29-37 recite densified particulate pharmaceutical compositions. Claims 29-30 and 33-37 are composition claims that are not limited by a particular use, nor are they limited to a particular class of pharmaceutical. Claims 31 and 32 are limited to densified particulate pharmaceutical compositions comprising a peptide/protein or gene construct, respectively, but these are not limited to a single recited use (see the plain language of the claims). Contrary to the Office's assertions, applicants have indeed provided sufficient detailed disclosure regarding how to make and use these compositions, and the rejection of these claims under Section 112 is deemed improper and simply not supported by the record.

More particularly, detailed directions are provided regarding how to convert a starting particulate pharmaceutical composition into densified particles, and how to assess those particles. See, e.g., applicants' specification at page 31, line 14 through page 34, line 16 and page 33, line 26 through page 36, line 3. Numerous uses of these densified particles are described throughout the specification, for example in Examples 1 and 2 (page 39, line 24 through page 47, line 7), applicants have provided working examples of how to make densified DNA pharmaceutical compositions using the methods of the invention, and then how to administer those compositions using needleless injection (i.e., how to use them). In Examples 3-5 (page 47, line 10 through page 50, line 9), applicants have provided working examples of how to make densified recombinant protein compositions using the methods of the invention, and then how to administer those compositions using needleless injection (again, how to use the densified compositions). And in Examples 8 and 9 (page 53, line 5 through page 55, line 27), applicants provided working examples of how to make densified particulate

compositions from commonly used pharmaceutical excipients using the methods of the invention.

When a composition claim is not limited by a recited use--as is the case with each and every one of applicants' claims 29-37--any enabled use that would reasonably correlate with the scope of those claims is sufficient to preclude a rejection for nonenablement based upon how to use. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). Applicants have clearly provided this enablement by way of their numerous working examples. In addition, since applicants' specification contains within it a connotation of how to use the recited invention (in needleless injection administrations) and the art recognizes that standard modes of administration are known and contemplated (e.g., numerous needleless injection techniques are known in the art), the requirements of 35 U.S.C. §112, first paragraph, are fully satisfied. See *In re Johnson*, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 144 USPQ 637,643 (CCPA 1965); and see also *In re Brana*, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).

For these reasons, then, the rejection of claims 29-37 under 35 U.S.C. §112, first paragraph, is improper. Reconsideration and withdrawal is earnestly solicited.

Scope of enablement for claims 39 and 40. Claim 39 recites a unit-dosage container for a needleless syringe that contains a compacted particulate pharmaceutical prepared using the methods of the present invention. Claim 40 recites a method for delivering a compacted pharmaceutical prepared using the methods of the present invention, wherein the preparation is delivered to a cell or tissue using a needleless syringe. The Office has rejected these claims on the basis that they are not enabled. Applicants respectfully disagree.

As discussed above, applicants have provided sufficiently detailed teaching on how to convert a starting particulate pharmaceutical composition into densified particles, and how to assess those particles. See, e.g., applicants' specification at page

31, line 14 through page 34, line 16 and page 33, line 26 through page 36, line 3. Numerous uses of these densified particles are described throughout the specification, for example in Examples 1 and 2 (page 39, line 24 through page 47, line 7), where applicants have provided working examples of how to make densified DNA pharmaceutical compositions using the methods of the invention, and then how to administer those compositions using needleless injection. In Examples 3-5 (page 47, line 10 through page 50, line 9), applicants have provided working examples of how to make densified recombinant protein compositions using the methods of the invention, and then how to administer those compositions using needleless injection (again, how to use the densified compositions). On page 37, at lines 5-32, applicants have provided sufficient teaching and disclosure regarding how to select and fill (i.e., make) suitable unit-dosage containers and then how to assemble those unit dosages into needleless syringe devices. The working examples demonstrate how to use the particulate compositions in an actual working animal model system. Accordingly, applicants have provided more than sufficient guidance on how to make and use the inventions recited in claims 39 and 40 throughout their entire scope. The rejection of claims 39 and 40 under 35 U.S.C. §112, first paragraph, is thus improper, and reconsideration and withdrawal of the rejection is respectfully requested.

Response to the issues of gene therapy, nucleic acid immunization, and delivery of peptides raised by the Office. Pages 5-11 of the instant Action are directed entirely to the Office's perception that any and all methods of gene therapy and methods of nucleic acid immunization can not possibly be enabled due to a list of various factors. Surprisingly, this line of reasoning has been directed against applicants' claims (which are not methods of treating or methods of curing disease, rather applicants' claims are to methods of producing pharmaceutical formulations, and particulate pharmaceutical formulations with enhanced density characteristics).

To paraphrase, the Office has seen fit to reject applicants' method of production claims, and particulate pharmaceutical claims, on the basis that some particulate compositions prepared using applicants' recited methods may not yield certain "desired therapeutic effects" and that "there is no guidance regarding how to treat AIDS, cancers. or genetic disorders" (Office Action at page 5); or there are "several factors that limit effective long-term or stable gene therapies" and that "certain genetic vectors may someday prove to be crude when compared to future developments" (Office Action at page 6); or "the fate of delivered gene transfer vectors .... level and duration of therapeutic effects" is unknown and "specific vector targeting techniques are not predictable" (Office Action at pages 7 and 8); or that there is "little evidence that nucleic acid immunization vaccines will be completely protective ... in any and all vertebrate subjects" (Office Action at pages 9 and 10); or that the specification fails to provide a demonstration that desired therapeutic results can be attained with any and all densified peptide/protein pharmaceuticals (Office Action at pages 10 and 11).

In response, applicants direct the Office's attention to the claims that are pending in the instant case. There are no claims to methods of treating, curing or completely protecting any and all diseases. There are no claims to compositions that have these features. Accordingly, all of the above-noted rejections have no real applicability to the claims at issue.

What applicants have disclosed and claimed are methods that can be used to convert particulate pharmaceuticals to densified particles that are suitable for delivery using needleless delivery. The Office can review the PDR or any other suitable pharmacopeia and find literally multiple hundreds of peptide/protein pharmaceutical compositions that are provided in lyophilized or spray-dried form and are sold and approved for numerous therapeutic or prophylactic uses. Any of these known

compositions can be converted to a densified composition using applicants' recited methods, and the skilled artisan, using the detailed instruction provided by applicants' specification can then readily administer those converted pharmaceuticals and would expect to obtain the desired therapeutic effect. Likewise, with DNAs for gene therapy or genetic immunization, there are numerous suitable vector systems currently in clinical trails and which are administered to achieve a desired physiological effect. Any of these known compositions can be converted into a densified composition using applicants' recited methods, and the skilled artisan would again be able to readily administer those converted pharmaceuticals and would expect to obtain the same sort of desired effect.

What the Office seems to be requiring is that in an invention that is in reality a generic method for making pharmaceutical compositions, enablement will not be met unless and until an applicant has converted all known or future pharmaceuticals over to the new form, and then tested each of those compositions for safety and efficacy. There is quite simply no basis for this sort of requirement under Section 112. In fact, applicants submit that such a requirement is obviously improper since it would discourage inventors from disclosing and teaching their discoveries for the public's benefit until an exhaustive experimental study into any and all possible embodiments or possible uses of their invention had been completed, which discouragement is antithetical and in direct contradiction of the guiding principals underlying Section 112. See, e.g., *Rohm & Hass Co. v. Dawson Chemical Co.*, 217 USPQ 515, 563-564 (S.D. Tex. 1983), *rev'd on other grounds*, 220 USPQ 289 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

The Rejections Under 35 U.S.C. §112, second paragraph:

Claims 24 and 40 were rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, the Office had objected that use of the phrase "and/or" in claim 24 rendered that claim indefinite, and noted that claim 40 depended from itself. Correction was required.

In response, applicants direct the Office's attention to the amendments made to claims 24 and 40 , wherein these issues have been corrected. Reconsideration and withdrawal of the rejection of claims 24 and 40 under 35 U.S.C. §112, second paragraph, is thus respectfully requested.

The Rejection Under 35 U.S.C. §102(b):

Claim 38 stands rejected under 35 U.S.C. §102(b) as unpatentable over Sanford. In particular, the Office asserts that Sanford "disclosed the making of inert particles including gold, tungsten or other metal spheres ... coated with nucleic acids such as DNA and RNA of the appropriate size and density ... and thus anticipates the claim." The basis for this rejection is the Office's perception that ballistic gold or other metal particles are "a pharmaceutically acceptable excipient" and would thus fall under the literal language of the claim. Applicants respectfully traverse the rejection.

In particular, applicants draw the Office's attention to the specification at page 16, line 29 through page 17, line 16 where the term "excipient" is expressly defined. At page 16, lines 3-4, applicants state "these terms [excipients] do not encompass biolistic core carriers." These excluded "biolistic core carriers" are themselves expressly defined in applicants's specification at page 20, lines 13-24, and thus it can be seen that gold, tungsten, platinum, ferrite, etc. materials are expressly excluded from the scope of claim 38.

Anticipation of a claim under §102 *requires* that each and every element of the claims be inherent in, or disclosed expressly by the anticipating reference. *Constant v. Advanced Micro-Devices, Inc.*, 7 USPQ2d 1057, 1064 (Fed. Cir. 1988). Claim 38, as expressly drafted, excludes the gold, tungsten, or other metal spheres as disclosed by Sanford. Accordingly, the compositions described by Sanford are not encompassed by applicants' claims, in fact are expressly excluded therefrom, and Sanford cannot possibly anticipate claim 38 under Section 102. Reconsideration and withdrawal of the rejection of claim 38 under 35 U.S.C. §102(b) is thus respectfully requested.

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CONCLUSION

Applicants submit that the claims define an invention which is both novel and nonobvious over the prior art. Accordingly, a Notice of Allowance is believed in order and the issuance of such a notice is respectfully requested. Applicants further ask that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that he contact the undersigned at (510) 742-9700, ext. 209.

Respectfully submitted,

Date: 26 June 2001

By: _____
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